

## IV-O-5.5

### **PIVOTAL ROL OF GUANINE NUCLEOTIDE EXCHANGE FACTOR, BETA-PIX IN LYSOPHOSPHATIDIC ACID (LPA)-MEDIATED CELLULAR SIGNALING DURING MOUSE NEUROGENESIS**

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#### **Abstract**

Lysophosphatidic acid (LPA) is a phospholipid growth factor that affects various cell functions, including cell proliferation and differentiation. LPA also has been known to play a pivotal role in neurogenesis and its neurogenic activity has been correlated, at least in part, with neuronal signaling triggered by LPA. Although there has been a number of evidences that argue an involvement of LPA in neurogenesis, molecular mechanisms underlying this developmental process has not been elucidated yet. The beta-pix is a guanine nucleotide exchange factor for Rho GTPases and interacts with PAK via the beta-pix SH3 domain. Beta-pix and PAK partly mediate cell proliferation and cytoskeletal rearrangements. Therefore, we reasoned that beta-pix might play a role in LPA-mediated neurogenesis. To test whether beta-pix is involved in LPA signaling cascades during neurogenesis, we isolated brain tissues obtained from neuron specific beta-pix null mice. By western blot analysis, we confirmed deficiency of the neuron-specific isoform of beta-pix in the neocortex and hippocampus of beta-pix null mice. However, we unexpectedly observed that a p85 beta-pix protein was highly expressed in the beta-pix null mice forebrain. When we measured the level of several MAP kinases, we found that the activity of P38 and JNK MAPK were increased in the brain tissue from null animals. Moreover, BrdU and p-histoneH3 immunostaining experiments revealed increases in neuroprogenitor cells within the dentate gyrus region of the null mice. Finally, to further examine whether beta-pix is involved in LPA signaling during brain development, we injected LPA into the lateral ventricle of E.13.5 embryonic mouse brains that lack beta-pix gene and evaluated their brain phenotype. Our study would provide insight for molecular mechanisms underlying LPA-mediated neurogenesis and involvement of the guanine nucleotide exchange factor, beta-pix.